UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/900,220	07/24/97	MIAO	N	ONV044.01

HM12/0807

PATENT GROUP
FOLEY HOAG AND ELIOT
ONE POST OFFICE SQUARE
BOSTON MA 02109

EXAMINER	
WILSON, M	
ART UNIT	**PAPER NUMBER**
1633	28

DATE MAILED: 08/07/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/900,220	Miao et al.
Examiner	**Group Art Unit**
Wilson, Michael C.	1633

☒ Responsive to communication(s) filed on *May 12, 2000* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-74* is/are pending in the application.

Of the above, claim(s) *1-34, 41, 47, 48, 55-61, and 71* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *35-40, 42-46, 49-54, 62-70, and 72-74* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *21*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ Notice to Comply

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The amendments filed 4-10-00, paper number 25, and 5-12-00, paper number 26, have been filed. Claims 49-74 have been added. Claims 1-74 are pending.

The IDS filed 6-16-2000 has not been entered because the PTO-1449 has not been received. It appears as though some references have been received. A copy of the IDS submission, fees charged, mail date receipt if any and the PTO-1449 is requested.

Election/Restriction

1. Applicant's election of Group IV claims 35-40 and 42-48 in Paper No. 19 filed 11-29-99 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Applicants election of the species SEQ ID NO:7 and 8 is acknowledged. Claims directed toward antisense (claims 47 and 48) and embodiments of the claims that encompass antisense are considered non-elected subject matter and are patentably distinct from the elected species of DNA for reasons of record. Newly added claims 49-74 are drawn to both elected and non-elected inventions. Claims 1-34, 41, 55-61 and 71 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 9 filed 11-29-99. Claims 35-40, 42-54, 62-70 and 72-74 are under consideration as they relate to nucleic acids encoding SEQ ID NO:7 and 8.

Specification

The specification contains numerous spelling errors (e.g. page 3, line 13, "administration"; page 4, line 26, "aspecf"; page 60, line 18 "re", line 35, "wew"). Correction is required.

Sequence Listing

The sequence listing is correct and has been entered. However, the application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2) but fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. **Sequences in the specification do not have SEQ ID Nos. e.g. pages 30-32, 42, 54 and 63.** If the sequence are not part of the sequence listing that has been entered, applicants must file a new "Sequence Listing" accompanied by directions to enter the listing into the specification as an amendment and provide statements regarding sameness and new matter with regards to the CRF and the "Sequence Listing." If the sequences are part of the entered sequence listing, the specification should indicate the proper SEQ ID NO: for each sequence.

Claim Rejections - 35 USC § 101

2. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 35-40, 42-46, 49-54, 62-70 and 72-74 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility. Claims 35-40, 42-46, 49-54, 62-70 and 72-74 are directed toward a nucleic acid sequence encoding a protein that is at least 95% identical to (or "corresponds to") SEQ ID NO:16 or 17, or fragments thereof that bind *patched* protein, regulate differentiation of neuronal cells, regulate survival of differentiated neuronal cells, regulate proliferation of chondrocyte, regulate proliferation of testicular germ line cells or functionally replace drosophila hedgehog. Claim 38 is directed toward a nucleic acid sequence encoding a bioactive human hedgehog protein. Claim 49 is drawn to SEQ ID NO:17 or fragments thereof that bind patched protein. Claim 63 is drawn to any nucleic acid sequence encoding human Desert hedgehog protein. The nucleic acid sequences encoding human Desert and Indian hedgehog proteins do not have a utility because the specification does not teach the human Desert and/or Indian hedgehog proteins function. The mere binding of human Desert or Indian hedgehog to patched is not of use by itself because the binding to patched acts in a pathway to cause an effect. The specification does not teach the binding of human Desert or Indian hedgehog to patched protein or the resulting effect from such binding. The specification does not teach the homology between human Desert and Indian hedgehog proteins and any other proteins for which the function is known. Therefore, it is not clear that the nucleic acids encoding the proteins have a disclosed use.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 35-40, 42-46, 49-54, 62-70 and 72-74 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification teaches the nucleic acid sequence of human Sonic, Indian and Desert hedgehog protein (SEQ ID NO:6-8 and 15-17) and that human Sonic hedgehog binds patched and effects neural development. The specification does not teach that the proteins encoded by SEQ ID NO:16 or 17, or fragments thereof have the functions claimed. The specification does not teach other sequences encoding human Desert hedgehog protein. Therefore, the limited information provided in the specification does not reasonably convey to one of skill in the art that Applicants were in possession of any and all nucleic acid sequences encoding any human hedgehog protein, any human Desert protein or any fragments of SEQ ID NO:16 or 17 that have the function claimed. Thus, it is concluded that the written description requirement is not satisfied for the claimed genus or for any species within the genus.

4. Claims 35-40, 42-46, 49-54, 62-70 and 72-74 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

Applicants are claiming nucleic acids encoding human Indian hedgehog protein (Ihh) and desert hedgehog protein (Dhh). The state of the art at the time of filing was such that little was known about hedgehog proteins other than Shh. Hammerschmidt teaches that mouse Ihh is expressed in developing cartilage and intestinal epithelium while mouse Dhh is expressed in the testes and is required for spermatogenesis (Hammerschmidt et al., 3-15-96, Genes & Development, Vol. page 647, column 1, last paragraph). The art at the time of filing did not teach the function of human Ihh or Dhh.

The specification teaches the nucleic acid sequence of the human sonic hedgehog (Shh), Ihh and Dhh (SEQ ID NO:6-8). The specification discusses the usefulness of Shh protein in neural development (see also Wang et al. 1995, Nature Med., Vol. 1, pages 1184-1188). The specification does not teach the function of Ihh or Dhh. The specification does not teach the homology between human Ihh or Dhh to any other hedgehog protein. Therefore, it is not clear that the function of human Ihh or Dhh is the same as mouse Ihh or Dhh or as human Shh. Given the teachings in the specification taken with the state of art at the time of filing regarding the function of human Ihh and Dhh, and the lack of correlation between human Dhh or Ihh to any

other hedgehog protein, it would have required one of skill undue experimentation to determine how to use the nucleic acids claimed.

Claims 35 and 36 recite possible functions of the proteins claimed are to bind *patched* protein, regulate differentiation of neuronal cells, regulate survival of differentiated neuronal cells, regulate proliferation of chondrocyte, regulate proliferation of testicular germ line cells or functionally replace drosophila hedgehog. Claim 36 recites the limitation of determining nucleic acids that hybridizes under stringent conditions to a nucleic acid sequence of SEQ ID NO: 7 or 8 that "corresponds" to a natural proteolytic product of a hedgehog protein and have such functions. While mouse Ihh is expressed in developing cartilage and intestinal epithelium while mouse Dhh is expressed in the testes and is required for spermatogenesis, such information may not correlate to human Ihh and Dhh which may have a different sequence and different function. Mouse Dhh expression may be required for spermatogenesis, but it is not clear how such information correlates to regulating proliferation of testicular germ cell lines as claimed. The mere binding of human Desert or Indian hedgehog to patched is not of use by itself because the binding to patched acts in a pathway to cause an effect. The specification does not teach the binding of human Desert or Indian hedgehog to patched protein or the resulting effect from such binding. The specification does not teach how to identify nucleic acids encoding proteins that are at least 95% identical, "corresponds" to or is a fragment of SEQ ID NO:16 or 17 such that the protein obtained is of use. Therefore, the specification does not enable one of skill to use any of the nucleic acids claimed.

The specification does not teach how to obtain nucleic acids encoding Ihh or Dhh protein fragments with any function that is of use, the stringency conditions required to obtain nucleic acids that encode the proteins claimed or how such proteins correspond to a natural proteolytic product of a hedgehog protein. Since the specification does not enable one of skill to determine the function of the human Dhh or Ihh for reasons above, the specification does not enable one of skill to use the nucleic acids to make a protein that binds *patched* protein, regulates differentiation of neuronal cells, regulates survival of differentiated neuronal cells, regulates proliferation of chondrocyte, regulates proliferation of testicular germ line cells or functionally replaces drosophila hedgehog as claimed.

Claim 44 recites the limitation of a "substantially purified oligonucleotide;" however, the specification does not define what applicants consider "substantial" and the term may have various meanings in the art. Therefore, it would require one of skill undue experimentation to determine whether applicants had obtained the desired oligonucleotide. The specification does not enable one of skill to determine what applicants consider about 19kD (claim 51) or how such fragments are of use. Claims 69 and 70 recite the limitation of introducing the nucleic acid into a host. Claims 40, 54 and 74 are directed toward a host cell. The only host or host cell that is enabled in the instant application is an isolated cell because applicants have not taught how to use the nucleic acids encoding human Ihh or Dhh or fragments of such nucleic acids *in vivo*. Claim 36 recites the limitation of stringent conditions and claim 72 recites the limitation of "high stringency conditions". However, the specification does not teach the stringency conditions that are

considered high or the conditions required to obtain a nucleic acid sequence encoding a human Dhh or Ihh protein that is of use. Without such guidance, it would require one of skill undue experimentation to determine the stringency conditions required to obtain a protein of interest.

Therefore, in view of the lack of guidance in the specification regarding how to use human Ihh or Dhh, the lack of correlation between human and non-human Ihh or Dhh and between human Shh and Ihh or Dhh, the lack of knowledge in the art regarding the function of human Ihh or Dhh, the examples provided and the breadth of the claims, the ordinary artisan at the time of the instant invention would not have known how to use the claimed invention with a reasonable expectation of success.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 49-53 and 72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 49-53 are indefinite because it is not clear whether the "fragment thereof" refers to the amino acid sequence or the nucleic acid sequence. It is unclear whether the amino acid sequence or the nucleic acid sequence binds ptc.

The phrase "capable of" in claim 53 is indefinite because it is unclear whether the vector replicates. "Capable of" implies a latent property and the conditions for obtaining the latent

property must be clearly defined. The claims do not clearly recite the conditions for obtaining vector replication. Therefore, it is unclear if the latent property is ever obtained.

The term "about" in claim 51 is indefinite because it is not clear if applicants consider a range of 18-20 kD about 19kD or a range of 14-24 kD about 19kD. Therefore, the metes and bounds of the term cannot be determined.

Claim 72 is indefinite because the specification does not define what applicants consider "high stringency conditions" and the definition of such conditions may vary in the art. Therefore, the metes and bounds of the conditions that are highly stringent cannot be determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following art rejections are based on the fact that the proteins taught in the art would at least bind non-specifically to *patched* protein.

6. Claims 35-38 and 44-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Marigo (GenEmbl., Acc. L38517, Feb. 12, 1995). Nucleotides 5-1276 of L38517 are 100% identical to nucleotides 351-1622 of SEQ ID NO:7. Therefore, the nucleic acid sequence taught by Marigo anticipates the nucleic acid claimed.

7. Claims 35-40 and 42-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Marigo (Marigo et al. 1995, Genomics, Vol. 28 pages 44-51).

Marigo teach cloning a nucleic acid sequence encoding the human Indian hedgehog protein and expressing the protein (page 45, column 1, isolation of human hedgehog cDNA clones). The protein produced by Marigo is 99.4% homologous to the protein of SEQ ID NO:16. Marigo teach making a human IHH labeled probe (page 45, column 1, last paragraph). Therefore, the nucleic acid sequence taught by Marigo anticipates the nucleic acid claimed.

8. Claims 38-46, 49-54, 63-70 and 72-74 are rejected under 35 U.S.C. 102(b) as being anticipated by Hillier (Hillier et al., 1996, Genome Res., Vol. 6, pages 807-828).

Hillier teaches the nucleic acid sequence encoding the human desert hedgehog precursor. The sequence is greater than 95% homologous to SEQ ID NO:8 from nucleotide 25-310 which a encodes a fragment of SEQ ID NO:17. Therefore, the nucleic acid sequence taught by Hillier anticipates the nucleic acid claimed.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson whose telephone number is (703) 305-0120. The examiner can normally be reached on Monday through Friday from 8:30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. The fax phone number for this Group is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

Michael C. Wilson

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Application No.: 08/900220

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other: _____

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing". (if necessary)

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification. (if necessary)

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE